REMARKS

A. Status of the Claims

Claims 29, 31–38, 47, and 57–60 were pending at the time of the Action. Claims 29 and 47 have been amended to recite that the proBNP fragments are Nt-proBNP fragments. In addition, claim 29 has been amended to recite that the antibody binds to at least one epitope in the Nt-proBNP region of canine proBNP. Support for this amendment may be found in the specification at, for example, page 5, lines 21-25. Claim 29 was also amended by deleting the phrase "or urine." Claims 31 and 57 have been amended to identify the amino acid sequences by SEQ ID NO. Claim 59 has been canceled, and claim 60 has been amended to depend from claim 29. Thus, claims 29- 31-38, 47, 47-58, and 60 are now pending.

B. Objection to the Drawings

The Action objects to the italics used in FIGs. 1B and 2B. Applicants have removed the italics in FIG. 1B, as well as in FIG. 2B. Applicants respectfully request the withdrawal of this objection in view of the amendment to the drawings submitted herewith.

C. The Rejections Under 35 U.S.C. § 112, First Paragraph

The Action rejects claims 29, 31–38, 47, and 57–60 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description and enablement requirements. The Action's arguments for both rejections are based largely on statements made in the Boswood Declaration regarding the state of the art prior to the disclosure in the present specification. The Action interprets these statements to mean that it was so unpredictable whether any antibody raised against an epitope within the N-terminal region of canine proBNP will bind canine proBNP in a blood sample that an inventor cannot satisfy the written description and enablement requirements for an antibody absent a working example demonstrating antibody

binding in a canine blood sample. Applicants respectfully disagree and submit that the claims satisfy the written description and enablement requirements of 35 U.S.C. § 112.

The Boswood Declaration makes the point that it was unclear whether the N-terminal region of canine proBNP would be present and detectable in the circulation. The Boswood declaration does not, however, support the Action's position that every antibody that binds within the N-terminal region is unpredictable. At the time the application was filed, it was generally known that human BNP was synthesized as a preprohormone (preproBNP), which was cleaved to form a signal peptide and proBNP (Boswood Declaration, para. 3). Human proBNP is then further cleaved into an N-terminal region (NT-proBNP) and a C-terminal region (BNP-32) (Boswood Declaration, para. 3). Several test kits for detecting human proBNP or fragments thereof were available (Specification, p. 3, ln. 30-32). While it was generally believed that canine BNP was also processed from preproBNP to proBNP to NT-proBNP and an active BNP fragment (*see, e.g.,* Liu *et al.*, *Gene* 292:183-90 (2002)), it was not known whether the N-terminal region of proBNP was present in detectable quantities in canine blood or if its presence could be associated with heart disease.

Based on a number of interspecies differences, the Boswood Declaration concluded that even though certain regions, including the N-terminal region, of BNP could be detected with antibodies in human circulation, it was still unpredictable whether the N-terminal region could be detected with antibodies in the circulation of dogs (*see* Boswood Declaration, para. 14 and 19). Thus, the Boswood Declaration establishes that the unanswered question prior to the disclosure in the present application was whether an N-terminal region or an NT-proBNP form of proBNP was present and detectable in canine circulation. The present specification answered that question.

The working examples in the specification demonstrated that the N-terminal region of proBNP was detectable in a canine blood sample using antibodies. Specifically, antibodies that bind within Epitopes 2 (SEQ ID NO: 2) and 5 (SEQ ID NO: 5) (*see* FIG. 1B) detected the N-terminal region of proBNP in canine blood samples as described at pages 11-12 and Table 2. In addition, the specification demonstrated that the amount of the N-terminal region of proBNP in canine blood samples could be used to diagnose cardiac insufficiency. *Id.* The amino acid sequence of Epitope 3 (SEQ ID NO: 3), which is described in the specification and recited in the current claims, is in between Epitope 2 (SEQ ID NO: 2) and Epitope 5 (SEQ ID NO: 5). A person of ordinary skill in the art would reasonably expect that an epitope in the amino acid sequence of SEQ ID NO: 3 would be present in a canine blood sample at least because it is located between SEQ ID NOs: 2 and 5, which were shown to be detectable in canine blood. Thus, the specification discloses the claimed invention and teaches a person of ordinary skill in the art how to make and use it without undue experimentation.

In addition, Applicants are concurrently filing a second declaration from Dr. Farace ("Second Farace Declaration"), which demonstrates that an antibody encompassed by the currently elected species can detect canine proBNP in a sample of canine plasma. Specifically, studies performed by Dr. Farace at Idexx Laboratories, which is a licensee of the technology claimed in this application, showed that an antibody raised against the amino acid sequence of KDAVSELQAEQLALEPL can successfully recognize and bind to canine proBNP that is present in a canine plasma sample. *See* Second Farace Declaration at ¶ 4. The sequence of SEQ ID NO: 3 is identical to the sequence KDAVSELQAEQLALEPL described in the Second Farace Declaration.

In view of the above, one of skill in the art reading the specification would reasonably conclude that the inventors were in possession of the claimed invention. *See* MPEP § 2163 ("To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention."). Additionally, the specification provides a disclosure sufficient to teach a person of ordinary skill in the art how to make and use the invention without undue experimentation. Applicants, therefore, respectfully request the withdrawal of the written description and enablement rejections.

D. The Claims Are Definite

The Action rejects claims 29, 32-38, 47, and 58-60 as allegedly being indefinite under 35 U.S.C. § 112, second paragraph. In particular, the Action contends that the phrases "amino acids 20 to 86" and "amino acids 32-48" are unclear. The current claims have been amended to remove these phrases.

The sequence described as "amino acids 32-48" is now described with reference to SEQ ID NO: 3. In addition, claim 29 now recites contacting the sample with at least one antibody that binds to at least one epitope in the Nt-proBNP region of canine proBNP. The Nt-proBNP region is discuss in the specification at, for example, page 5, lines 21-25. Furthermore, the sequence and location of the cleavage site in canine proBNP, which cleaved proBNP in to Nt-proBNP and an active BNP fragment, was known in the art (*see, e.g.,* Liu *et al.*, *Gene* 292:183-90 (2002)). Thus, a person of ordinary skill in the art would understand what is meant by the Nt-proBNP region of canine proBNP.

In view of the above, Applicants respectfully request the withdrawal of this rejection.

E. The Rejections Under 35 U.S.C. § 103(a)

1. MacDonald in view of Asada, Harlow & Lane, Janeway, and Wolfe

The Action rejects claims 29, 31–33, 37–38, 47, and 57–59 as allegedly obvious over MacDonald in view of Asada *et al.*, Harlow & Lane, Janeway *et al.*, and Wolfe. Applicants traverse this rejection.

To establish a *prima facie* case of obviousness the Action must, among other things, establish that there would have been a reasonable expectation of success to achieve the claimed invention. Evidence available prior to the filing of the present disclosure indicated that studies regarding BNP in one species would not predictably translate to a different species. In particular, it was not previously known whether the N-terminal region of canine proBNP circulated in blood in amounts sufficiently abundant and/or stable to be detected by immunoassay. For example, Thomas *et al.* stated:

> BNP differs across species, with only short segments retaining sequence homology. In addition, there are species-specific variations in the structure of the non-guanylyl cyclase-linked natriuretic peptide C (NP_C) receptor or clearance receptor, which is likely to affect the metabolism of BNP.

Thomas *et al.*, p. 369, col. 2 (2003) (IDS Reference C16) (emphasis added); *see also* Boswood Declaration at ¶ 10.

Thomas also disclosed that canine BNP-32 was far less stable than human BNP-32 in the circulation, with canine BNP-32 having a half-life of 90 seconds compared to human BNP-32 having a half-life of 22 minutes (Thomas, p. 373, col. 1). Additionally, Goetze *et al.* (2004) (IDS Reference C14) reported that the cleavage site corresponding to positions 73-76 in the human sequence is not well conserved across species (Goetze, p. 1505, Fig. 2). Accordingly, these publications indicated the likelihood that BNP is metabolized differently across species. *See* Boswood Declaration at ¶ 10.

It was also known that observations concerning BNP in human plasma did not always hold true for BNP in canine plasma. MacDonald reported that plasma BNP increases with age in humans, but there is no correlation between plasma BNP and age in dogs (p. 175, col. 1). Thus, that study demonstrated that not all observations regarding circulating concentrations of human BNP could be extrapolated to canine BNP. Boswood Declaration, para. 17.

The disclosures in the MacDonald, Asada, Harlow & Lane, and Wolfe references do not provide a reasonable expectation of success. MacDonald does not provide any data or discussion of NT-proBNP in canines. Rather, MacDonald discloses data that suggests a correlation between BNP-32 levels and mitral valve disease or congestive heart failure in canines. MacDonald states that the veterinary profession would benefit from a simple diagnostic test that would help identify patients with heart disease (p. 176, left column, last paragraph), but MacDonald does not claim to provide such a test. In fact, MacDonald states that further studies are needed to verify their results (p. 175, right column, last paragraph).

Asada reported that BNP exists primarily in human blood as proBNP rather than BNP-32 and, therefore, Asada said that it is important to assay both proBNP and BNP-32 in humans. Asada, however, does not teach whether the N-terminal region of proBNP exists in a stable and detectable form in canine blood.

Harlow & Lane is a laboratory manual that provides general guidelines for making and using antibodies. It does not provide any specific guidance for making antibodies to canine proBNP. Wolfe is cited for its teachings concerning the size of epitopes, and Janeway is cited for teaching that polyclonal antibodies constitute a homogeneous population of antibodies that bind immunogens in many different ways (Action, p. 17-18). Thus, Wolfe and Janeway also do not provide any specific guidance for making antibodies to canine proBNP. Furthermore, even if

a person would have selected a canine proBNP peptide for antibody production using one or more of the guidelines in Harlow & Lane and/or basing the peptide selection on the human peptide described by Asada, a person of ordinary skill in the art still would not have a reasonable expectation of success in using the antibody to detect the N-terminal region of canine proBNP in a blood sample and correlating the amount of protein detected with heart disease for the reasons discussed above.

For at least these reasons, claims 29, 31-33, 37-38, 47, and 57-59 are patentable over MacDonald *et al.*, Asada *et al.*, Harlow & Lane, Janeway *et al.*, and Wolfe *et al.* Applicants, therefore, respectfully request withdrawal of the rejection.

2. MacDonald in view of Asada, Harlow & Lane, Janeway, Wolfe, and Harlow & Lane 2

Dependent claims 34-36 are rejected as allegedly unpatentable over the MacDonald, Asada, Harlow & Lane, Janeway, and Wolfe references discussed above, further in view of Harlow & Lane 2. Applicants traverse this rejection.

If an independent claim is nonobvious under 35 U.S.C. § 103(a), then any claim depending therefrom is nonobvious. MPEP § 2143.03. For the reasons discussed in the preceding section, claims 29, 31-33, 37-38, 47, and 57-59 are non-obvious over MacDonald, Asada, Harlow & Lane, Janeway, and Wolfe. Harlow & Lane 2 is cited for its general teachings concerning antibody labeling, thus Harlow & Lane 2 does not address any of the other deficiencies discussed above with respect to the independent claims. Accordingly, dependent claims 34-36 are also non-obvious.

3. *MacDonald in view of Asada, Harlow & Lane, Janeway, Wolfe, and Hrubec*

Claim 60 is rejected as allegedly obvious over MacDonald, Asada, Harlow & Lane, Janeway, and Wolfe references discussed above, further in view of Hrubec. Applicants traverse this rejection.

If an independent claim is nonobvious under 35 U.S.C. § 103(a), then any claim depending therefrom is nonobvious. MPEP § 2143.03. For the reasons discussed in the preceding section, claims 29, 31-33, 37-38, 47, and 57-59 are non-obvious over MacDonald, Asada, Harlow & Lane, Janeway, and Wolfe. Hrubec is cited for its general teachings concerning biochemical analysis of plasma or serum, thus Hrubec does not address any of the other deficiencies discussed above with respect to the independent claims. Accordingly, dependent claim 60 is also non-obvious.

4. *Rejections over MacDonald in view of Karl and Liu*

Claims 29, 31-38, 47, and 57-60 are rejected as allegedly unpatentable over MacDonald in view of Karl *et al.* and Liu *et al.* Applicants traverse this rejection.

As discussed above, MacDonald discloses data that suggests a correlation between BNP-32 levels and mitral valve disease or congestive heart failure in canines. MacDonald states that the veterinary profession would benefit from a simple diagnostic test that would help identify patients with heart disease (p. 176, left column, last paragraph), but MacDonald does not claim to provide such a test. Rather, MacDonald states that further studies are needed to verify their results (p. 175, right column, last paragraph). Moreover, MacDonald does not provide any data or discussion of NT-proBNP in canines.

The Action alleges that it would have been obvious to modify the method of MacDonald to detect the N-terminal region of proBNP instead of BNP-32 in view of the teachings of Karl.

In particular, the Action states that Karl raised antibodies against amino acids 30-38 of human NT-proBNP and, therefore, it would have been obvious to raise antibodies that bind within the corresponding region of canine NT-proBNP (Action, p. 24). The Action further cites Liu as showing that amino acids 30-38 in human proBNP correspond to amino acids 37-45 in canine proBNP (subtracting the signal peptide) (Action, p. 27), and as teaching that there is strong similarity between human and canine proBNP (Action, p. 25).

Although Liu noted sequence similarity in mammalian BNP, Liu also stated that "human BNP was a distinct group as compared to the other species" (Liu, p. 187, paragraph spanning the left and right columns), and that that the "human prepropeptide has many unique sequences and appears to have evolved independently from other species." (Liu, p. 188, right column). Furthermore, it can be seen from the sequence alignments in Liu, that the sequences identified in the Action (*i.e.,* amino acids 30-38 in human proBNP and amino acids 37-45 in canine proBNP) are not identical.

Thomas *et al.* (IDS Ref. 16) states that the natriuretic peptides ANP and CNP have "strong homology across species," but BNP is different "with only short segments retaining sequence homology" (Thomas, p. 369, col. 2). Moreover, Liu teaches that ANP antibodies are universal, whereas antibodies of BNP are species-specific (Liu, p. 183, col. 2). Thus, both Thomas and Liu teach that BNP is an exception to the strong homology shown among other natriuretic peptides. The Farace Declaration filed with Applicants' response on May 18, 2010 ("First Farace Declaration"), also showed the lack of BNP structural similarity across species by demonstrating that antibodies directed to epitopes in canine NT-proBNP did not recognize human or cat NT-proBNP (First Farace Declaration, para. 2-6). Thus, the First Farace

Declaration provides additional evidence rebutting an assertion that there is strong sequence and structural similarity between human and canine NT-proBNP.

Regardless, even if a person of ordinary skill in the art had been motivated to obtain an antibody against amino acids 37-45 in canine proBNP, which Applicants dispute, the person still would not have had a reasonable expectation of success detecting canine proBNP, or a fragment thereof containing the amino acid sequence of SEQ ID NO: 3, in a canine blood sample. Evidence available at the time indicated that studies regarding BNP in one species would not predictably translate to a different species.

For example, Thomas *et al.* stated:

> BNP differs across species, with only short segments retaining sequence homology. In addition, there are species-specific variations in the structure of the non-guanylyl cyclase-linked natriuretic peptide C (NP_C) receptor or clearance receptor, which is likely to affect the metabolism of BNP.

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It was also known that observations concerning BNP in human plasma did not always hold true for BNP in canine plasma. MacDonald reported that plasma BNP increases with age in humans, but there is no correlation between plasma BNP and age in dogs (p. 175, col. 1). Thus,

that study demonstrated that not all observations regarding circulating concentrations of human BNP could be extrapolated to canine BNP. Boswood Declaration, para. 17.

To establish a *prima facie* case of obviousness the Action must, among other things, establish that there would have been a reasonable expectation of success to achieve the claimed invention. As discussed above, evidence available prior to the filing of the present disclosure indicated that studies regarding BNP in one species would not predictably translate to a different species. In particular, it was not previously known whether the N-terminal region of canine proBNP circulated in blood in amounts sufficiently abundant and/or stable to be detected by immunoassay. MacDonald did not provide any data or discussion as to whether the N-terminal region of proBNP is present and detectable in canine blood. While Karl reported that ***human*** NT-proBNP is more stable than BNP-32, Karl did not discuss the stability of ***canine*** NT-proBNP or BNP-32. In fact, Karl does not mention any applicability of the findings regarding human BNP to canine BNP, which is not surprising given the species-to-species variability that was known to exist for BNP molecules.

In view of the above, a person of ordinary skill in the art would not have had a reasonable expectation of success in view of the cited references. Thus, the current claims are patentable over MacDonald, Karl, and Liu. Applicants, therefore, request withdrawal of this rejection.

F. Double Patenting Rejection

Claims 29, 31-38, 47, and 57-60 are provisionally rejected for obviousness-type double patenting over claims 1-4, 6-12, and 21-22 of co-pending Application No. 12/394,731. In addition, claims 29, 31-38, 47, and 57-60 are provisionally rejected for obviousness-type double patenting over claims 1-4, 6-12, and 21-22 of co-pending Application No. 12/394,682 in view of Harlow & Lane, Karl, and Liu. . A provisional double-patenting rejection is not a final rejection that blocks the prosecution of all of the conflicting applications. If a provisional double-

patenting rejection is the only rejection remaining in the earlier filed application, the Examiner should withdraw the rejection and permit the application to issue as a patent without a terminal disclaimer. MPEP § 804(I)(B).

G. Conclusion

Applicants believe this to be a complete response to all issues raised in the Office Action dated July 20, 2011. The Examiner is invited to contact the undersigned attorney at (512) 536-5654 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

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